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This Month in *AJP*

TWEAKing Muscle Regeneration

Although skeletal muscle can regenerate *in vivo*, inflammatory molecules are thought to inhibit this process, resulting in muscle-wasting disease. Mittal et al (**Am J Pathol 2010, 177:1732–1742**) discovered that expression of proinflammatory cytokine TNF-like weak inducer of apoptosis (TWEAK) and its receptor Fn14 are increased in muscles after injury. TWEAK deficiency enhanced metrics of muscle regeneration and decreased levels of inflammatory mediators such as NF-κB, whereas induced TWEAK expression inhibited muscle regeneration as well as increased levels of inflammatory mediators. TWEAK inhibition may therefore provide a novel therapeutic target for muscle regeneration.

Antiviral $CD8^+$ T Cells Protect against Multiple Sclerosis

In a Theiler's murine encephalomyelitis virus (TMEV) model of multiple sclerosis, $CD8^+$ T cells specific for the immunodominant viral peptide protect against demyelinating disease. Using confocal microscopy and live tissue imaging, McDole et al (**Am J Pathol 2010, 177:1823–1833**) explored the interactions of virus-specific $CD8^+$ T cells with different cell types in the central nervous system. Antiviral $CD8^+$ T cells became activated in conjunction with infected neurons; these cells polarized their T cell receptors, CD8, and granzyme B toward infected neurons, despite low neuronal expression levels of MHC class I molecules. $CD8^+$ T cells also extended cytoplasmic processes to neurons, a mechanism thought to be involved in T cell migration. The direct interactions between $CD8^+$ T cells and neurons could mediate the protective role played by these cells in TMEV-mediated multiple sclerosis.

Prion Protein Mediates HIV-Associated Neuroinflammation

Nearly half of HIV-infected individuals develop neurocognitive impairment due to the presence of HIV in the central nervous system (CNS). Roberts et al (**Am J Pathol 2010, 177:1848–1860**) hypothesized that PrP^c (protease-resistant protein), the nonpathological cellular isoform of prion protein, plays a role in CNS disease associated with HIV infection. PrP^c levels were increased in the CNS of HIV-infected individuals, and PrP^c was secreted in the cerebrospinal fluid at levels comparable to that observed in individuals with neurocognitive impairment. Indeed, HIV infection altered the levels of PrP^c released from peripheral blood mononuclear cells. Moreover, PrP^c could induce neuroinflammation by inducing the production of inflammatory mediators by astrocytes. Taken together, these data suggest that PrP^c may provide a novel biomarker for HIV-associated cognitive decline and may play a direct role in mediating HIV-associated neuroinflammation.

Epigenetic Control of Fibrosis

Liver fibrosis, which is primarily mediated by hepatic stellate cells, is characterized by the suppression of matrix metalloproteinases (MMPs) and the coordinate accumulation of extracellular matrix. To determine the mechanism underlying MMP repression in liver fibrosis, Qin et al (**Am J Pathol 2010, 177:1915–1928**) examined key signaling pathways involved in MMP expression. They found that MMP transcription was inhibited due to impaired transcription factor recruitment via decreased levels of histone acetylation in hepatic stellate cells. This inhibition was accompanied by an accumulation of histone deacetylase 4, and histone deacetylase 4 expression in hepatic stellate cells resulted in decreased levels of MMP expression. Therefore, an epigenetic switch contributes to MMP repression in liver fibrosis.

AIP (Aryl Hydrocarbon Receptor-Interacting Protein) Mutation Predisposes to Pituitary Adenomas

Pituitary adenomas are benign tumors of the anterior pituitary gland that result in secretion of excess pituitary hormones such as growth hormone or prolactin. To further study pituitary adenomas, Raitila et al (**Am J Pathol 2010, 177:1969–1976**) generated a mouse model deficient in *AIP*, which has been correlated with predisposition to pituitary adenomas in humans. Mice heterozygous for *AIP* were strongly predisposed to developing growth hormone–secreting pituitary adenomas but not other tumor types, and these tumors presented with an aggressive phenotype. In addition, similar to human tumors, expression of aryl hydrocarbon receptor nuclear translocator 1 or 2 (ARNT or ARNT2) protein was lost in the mouse tumors. Thus, mice deficient in *AIP* provide a novel model to study human pituitary adenomas.